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Copper-Catalyzed Oxidative Dehydrogenative Carboxylation of Unactivated Alkanes to Allylic Esters via Alkenes

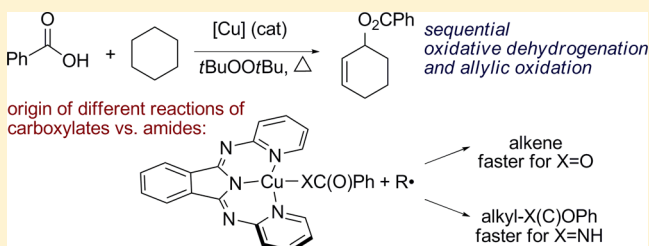
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Supporting Information

ABSTRACT: We report copper-catalyzed oxidative dehydrogenative carboxylation (ODC) of unactivated alkanes with various substituted benzoic acids to produce the corresponding allylic esters. Spectroscopic studies (EPR, UV-vis) revealed that the resting state of the catalyst is [(BPI)Cu(O₂CPh)] (1-O₂CPh), formed from [(BPI)Cu(PPh₃)₂], oxidant, and benzoic acid. Catalytic and stoichiometric reactions of 1-O₂CPh with alkyl radicals and radical probes imply that C–H bond cleavage occurs by a *tert*-butoxy radical. In addition, the deuterium kinetic isotope effect from reactions of cyclohexane and *d*₁₂-cyclohexane in separate vessels showed that the turnover-limiting step for the ODC of cyclohexane is C–H bond cleavage. To understand the origin of the difference in products formed from copper-catalyzed amidation and copper-catalyzed ODC, reactions of an alkyl radical with a series of copper–carboxylate, copper–amidate, and copper–imidate complexes were performed. The results of competition experiments revealed that the relative rate of reaction of alkyl radicals with the copper complexes follows the trend Cu(II)–amidate > Cu(II)–imidate > Cu(II)–benzoate. Consistent with this trend, Cu(II)–amidates and Cu(II)–benzoates containing more electron-rich aryl groups on the benzamidate and benzoate react faster with the alkyl radical than do those with more electron-poor aryl groups on these ligands to produce the corresponding products. These data on the ODC of cyclohexane led to preliminary investigation of copper-catalyzed oxidative dehydrogenative amination of cyclohexane to generate a mixture of *N*-alkyl and *N*-allylic products.



INTRODUCTION

The oxidation of alkanes to alcohols or ketones and the dehydrogenation of alkanes to alkenes are both widely studied targets for C–H bond functionalization.^{1–5} For example, the oxidation of cyclohexane to a mixture of cyclohexanol and cyclohexanone is a large-scale commercial process for the production of adipic acid.⁶ The oxidation of propene at the allylic C–H bond to form acrolein⁷ also is a well-known large-scale C–H bond oxidation process, and the oxidation of allylic C–H bonds to allylic esters is being studied actively for applications in target-oriented synthesis.^{8–17}

The dehydrogenation of light alkanes is being studied as a route to ethylene, propene, butene, butadiene, isobutene, and isoprene, with hydrogen as the single side product¹⁸ or with an oxidant to consume the hydrogen and make the reaction, called oxidative dehydrogenation (ODH), favorable thermodynamically.

Although alkane dehydrogenation and allylic oxidation are both known reactions, the combination of these two reactions in a single process is rare. One can envision that such a process could occur by initial dehydrogenation of an alkane to an alkene, followed by oxidation of allylic C–H bonds in the alkene product. Indeed, one form of such a reaction is the well-established synthesis of maleic anhydride from butane.¹⁹ However, the combination of dehydrogenation and selective

oxidation of the alkene to an allylic alcohol derivative directly from an alkane is poorly developed.

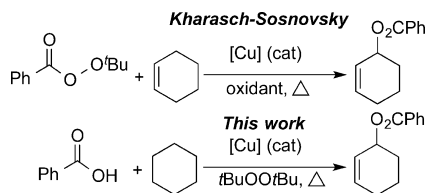
Recently, two examples of copper-catalyzed oxidative dehydrogenative cross-coupling reactions of an aldehyde and toluene with cyclohexane to generate allylic esters have been reported.^{20,21} However, the yields of these reactions were generally low and occurred with limited substrate scope. Moreover, the mechanisms of these reactions were not studied in depth. Copper-catalyzed combinations of alkane dehydrogenation and aziridination²² or epoxidation²³ also have been reported, but the epoxide and aziridine are just one component of a mixture of products, and they formed with a maximum of 3–4 turnovers. Thus, a high-yield combination of dehydrogenation and C–H bond oxidation of an alkane to form an allylic alcohol derivative that occurs with tolerance for a wide range of functional groups is not known.

Herein, we report the copper-catalyzed oxidative dehydrogenative carboxylation (ODC) of unactivated alkanes in the presence of carboxylic acid derivatives to form the corresponding allylic ester (Scheme 1). This reaction is related to the classic Kharasch–Sosnovsky reaction,²⁴ but the starting material is an alkane, rather than an alkene. The reactions occur by

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Scheme 1

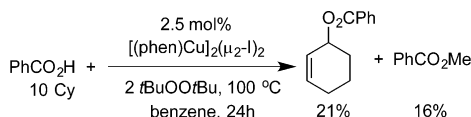


oxidative dehydrogenation of an alkane and oxidation of the resulting allylic C–H bond. Detailed mechanistic studies show that the *tert*-butoxy radical abstracts a C–H bond of cyclohexane to generate a transient cyclohexyl radical, and this radical is converted to cyclohexene by a copper–benzoate complex. The cyclohexene is then oxidized to form the allylic ester product. The relative rates for trapping of the radical by the ligand on copper versus conversion of the radical to an alkene control the selectivity for the formation of allylic vs alkyl ester products.

RESULTS AND DISCUSSION

1. Development of Intermolecular ODC of Cyclohexane. To extend our recently published copper-catalyzed amidation of cyclohexane to the acetoxylation or benzyloxylation of cycloalkanes, we conducted the reaction of cyclohexane with benzoic acid and *t*BuOO*t*Bu in the presence of [(phen)Cu](μ_2 -I)₂ (phen = 1,10-phenanthroline).²⁵ We envisioned that the combination of the Cu(I) and *t*BuOO*t*Bu should generate *t*BuO•, which could generate cyclohexyl radical, and this radical could combine with [(phen)Cu-(O₂CPh)₂]^{26,27} to form cyclohexyl benzoate. Although benzoic acid did react with cyclohexane and *t*BuOO*t*Bu in the presence of 2.5 mol% of [(phen)Cu](μ_2 -I)₂, this combination of materials yielded the allylic ester cyclohex-2-en-1-yl benzoate (21%) and methyl benzoate (16%), not the alkyl benzoate (Scheme 2). Cyclohexyl benzoate was not detected. Thus, the

Scheme 2. Initial Studies of ODC of Cyclohexane



reaction of cyclohexane with benzoic acid and *t*BuOO*t*Bu in the presence of copper occurs by a combination of dehydrogenation and C–H bond carboxylation.

To increase the yield of the allylic ester from this reaction, we evaluated the reactivity of benzoic acid (0.5 mmol) and cyclohexane (10 equiv) with a series of copper salts and discrete copper complexes. The results of these experiments are presented in Table 1. Simple Cu(I) and Cu(II) halides catalyzed the coupling of benzoic acid and cyclohexane to produce cyclohex-2-en-1-yl benzoate in moderate to good yields (entries 1–7). For example, the combination of CuCl (5 mol%) and *t*BuOO*t*Bu (3 equiv relative to benzoic acid) gave a high yield of product (76%). Reactions conducted with a higher 10 mol% loading of Cu occurred in a lower yield (54%) than did the reaction with 5 mol% copper (entry 4). A similar trend of lower yield with higher loadings of catalyst was observed for the copper-catalyzed amidation of cyclohexane.²⁸ The lower yield of product from reactions containing higher concentrations of copper presumably results from quenching of the

Table 1. Reaction Development of Catalytic ODC of Cyclohexane^a

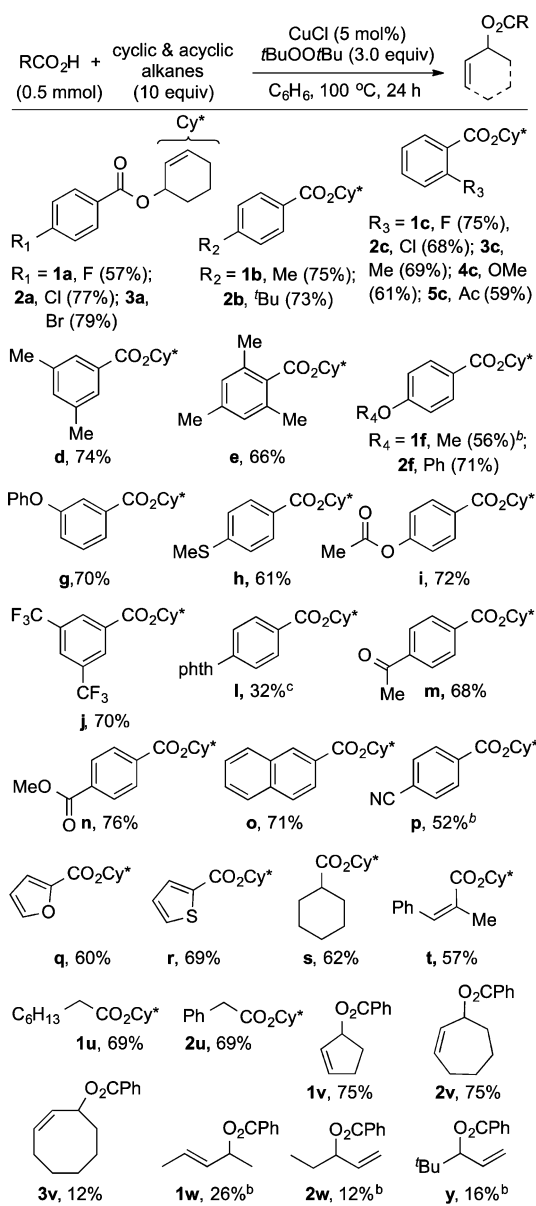
entry	catalyst ⁱ	oxidant	Yields ^a	
			A	B
1	CuCl	<i>t</i> BuOO <i>t</i> Bu	65	7
2 ^c	CuCl	<i>t</i> BuOO <i>t</i> Bu	76	4
3 ^d	CuCl	<i>t</i> BuOO <i>t</i> Bu	78	4
4 ^e	CuCl	<i>t</i> BuOO <i>t</i> Bu	54	5
5 ^f	CuCl	<i>t</i> BuOO <i>t</i> Bu	21	16
6	CuCl ₂	<i>t</i> BuOO <i>t</i> Bu	56	5
7 ^e	CuI	<i>t</i> BuOO <i>t</i> Bu	58	15
8	[(phen)Cu] ₂ (μ_2 -I) ₂	<i>t</i> BuOO <i>t</i> Bu	21	16
9	[(L1)CuCl]	<i>t</i> BuOO <i>t</i> Bu	40	15
10 ^g	[(BPI)CuCl]	<i>t</i> BuOO <i>t</i> Bu	48	17
11 ^h	[(BPI)CuCl]	<i>t</i> BuOO <i>t</i> Bu	50	20
12	[(BPI)CuCl]	<i>t</i> BuOO <i>t</i> Bu	46	16
13 ^g	[(BPI)Cu(PPh ₃) ₂]	<i>t</i> BuOO <i>t</i> Bu	47	17
14		<i>t</i> BuOO <i>t</i> Bu	np	np

^aConditions: 0.5 mmol of acid, 5.0 mmol of cyclohexane, 0.025 mmol of catalyst, 1.0 mmol of oxidant, 1 mL of C₆H₆ at 100 °C for 24 h. ^b¹H NMR yield with MeNO₂ as the internal standard added after reaction. ^c3 equiv of *t*BuOO*t*Bu. ^d4 equiv of *t*BuOO*t*Bu. ^e10 mol%. ^f1 equiv of *t*BuOO*t*Bu. ^g2.5 mol%. ^h48 h. ⁱL1, Me₂NCH₂CH₂N=CH (2-OH-C₆H₄); BPI, bis(2-pyridylimino)isoindole; phth, phthalimide. np = no product.

transient *tert*-butoxy radical by Cu(I) to form Cu(II)-O*t*Bu species.²⁹ The reaction requires both copper and oxidant (entry 14).

The reaction also occurred when catalyzed by Cu(I) complexes containing neutral bidentate nitrogen ligands, such as 4,7-dichloro-1,10-phenanthroline, 3,4,7,8-tetramethyl-1,10-phenanthroline, 1,10-phenanthroline, 4,7-dimethyl-1,10-phenanthroline, 4,5-diazafluoren-9-one, and 1,10-phenanthroline-5,6-dione.³⁰ The reactions catalyzed by these Cu(I) complexes ligated by dative nitrogen ligands formed cyclohex-2-en-1-yl benzoate (23–64%) in modest yields.³⁰ Reactions catalyzed by the well-defined [(L1)CuCl] (L1 = Me₂NCH₂CH₂N=CH(2-O-C₆H₄)), [(BPI)Cu(PPh₃)₂], and [(BPI)CuCl] (BPI = bis(2-pyridylimino)isoindole) reproducibly produced the product in 40–50% yields (entries 9–13). The reactions catalyzed by ligated copper complexes gave larger amounts of methyl benzoate than did reactions with unligated copper.³¹ Consistent with this observation, Kochi reported that nitrogen-ligated Cu(II) complexes oxidize alkyl radicals to alkenes more slowly than do simple Cu(II) salts.^{32,33} Although these reactions with ligated copper occurred in lower yield than those with simple copper halides, they did give substantial amounts of product and were valuable for studying the mechanism of this reaction (*vide infra*).

2. Scope of Intermolecular Oxidative Dehydrogenative Carboxylations of Alkanes. The scope of the ODC of cyclohexane with carboxylic acids to form allylic esters is presented in Table 2. The yields of these reactions are based on carboxylic acid. The mass balance consisted of unreacted carboxylic acid and methyl benzoate, the origin of which will be discussed later in the paper. The reaction is tolerant of halogens on the benzoic acid 4-X-C₆H₄-CO₂H (X = F (1a), Cl (2a), Br

Table 2. Intermolecular ODC Cyclic and Acyclic Alkanes to Allylic Esters^a

^aYields were determined by ¹H NMR spectroscopy with MeNO₂ as internal standard, added after the reaction, and reported as an average of two reactions. ¹H NMR chemical shifts were compared to authentic allylic ester products. ^b2.5 mol% of **1-PPh₃**, ^c5 mol% of **1-PPh₃**, MeCN. phth = phthalimide.

(**3a**)), forming the corresponding allylic esters in 57–79% yields in these cases. The reaction is also tolerant of a halide (**1c**, **2c**), methoxy (**4c**), and acetyl group (**5c**) in the *ortho* position. Carboxylic acids containing electron-donating substituents on the aromatic system, such as methyl (**1b,d,e**), *tert*-butyl (**2b**), methoxy (**1f**), 4-phenoxy (**2f**), and phthalimido (**1**) groups, generated the corresponding allylic ester products in 56–71% yields. Substrates containing electron-withdrawing substituents, such as acetyl (**m**), trifluoromethyl (**j**), cyano (**p**), and carboalkoxy (**n**) groups, also gave the corresponding products in moderate to good yields (52–76%). Even a thioether (**h**) is tolerated, despite the oxidizing conditions of

the catalytic reaction; cyclohex-2-en-1-yl 4-(methylthio)-benzoate was produced in 69% yield.

The reactions with heteroaryl carboxylic acids, such as furan (**q**) and thiophene (**r**), also gave substantial yields of allylic esters; however, pyridine carboxylic acids did not yield allylic oxidation products.

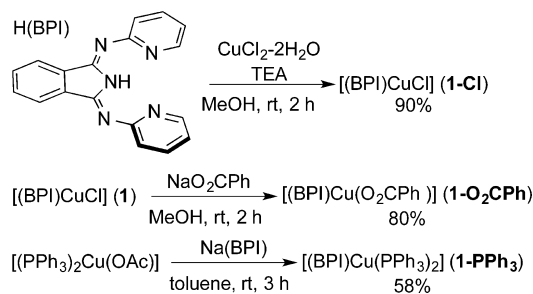
Finally, vinyl and aliphatic carboxylic acids reacted to form allylic esters. Specifically, the ODC of cyclohexane with cyclohexanecarboxylic acid (**s**), (*E*)-2-methyl-3-phenylacrylic acid (**t**), octanoic acid (**1u**), and phenylacetic acid (**2u**) gave cyclohex-2-en-1-yl cyclohexanecarboxylate (62%), cyclohex-2-en-1-yl (*E*)-2-methyl-3-phenylacrylate (57%), cyclohex-2-en-1-yl octanoate (69%), and cyclohex-2-en-1-yl 2-phenylacetate (69%), respectively.

The reaction also occurred with smaller or larger cycloalkanes and, to an extent, with acyclic alkanes. Reactions of benzoic acids with cyclopentane and cycloheptane in the presence of 5 mol% of CuCl yielded the corresponding products in good yield (cyclopent-2-en-yl benzoate (**1v**, 75%), cyclohept-2-en-yl benzoate (**2v**, 75%)), but the reaction with cyclooctane formed cyclooct-2-en-yl benzoate (**3v**, 12%) in modest yield. In addition to reactions of cyclic alkanes, reactions of linear alkanes (i.e., pentane) containing multiple C–H bonds were performed to assess the selectivity of the catalytic ODC. The reaction of pentane and benzoic acid in the presence of 2.5 mol% of **1-PPh₃** and *t*BuOO*t*Bu produced two products: pent-en-2-yl benzoate³⁴ (**1w**, 26%) and pent-1-en-3-yl benzoate³⁵ (**2w**, 10%). The potential product of pen-2-en-1-yl benzoate, which would be obtained from the oxidation of the pent-2-ene intermediate at the primary C–H bond, was not observed. This observation suggests that oxidation of a secondary allylic C–H bond is favored over oxidation of a primary allylic C–H bond. This relative reactivity is consistent with the relative C–H bond dissociation energies.³⁶ The reaction of 2,2-dimethylpentane and benzoic acid produced 4,4-dimethylpent-1-en-3-yl benzoate³⁷ (**y**, 16%) and methyl benzoate (80%) as the major byproduct.

3. Synthesis of Cu(I) and Cu(II) Complexes and Determination of the Resting State of the Catalyst.

Although most of the catalytic reactions were performed with CuCl as catalyst, copper complexes ligated by the imidobipyridine ligand BPI did catalyze the reaction, and the molecular complex [(BPI)Cu(O₂CPh)] (**1-O₂CPh**) was amenable to isolation. The soluble, single-component Cu(II) species **1-O₂CPh** was prepared in 80% yield as a green solid by salt metathesis between [(BPI)CuCl] (**1-Cl**) and NaO₂CPh in MeOH at room temperature for 3 h (Scheme 3). Elemental analysis of the product was consistent with the proposed atomic composition for **1-O₂CPh**. We suspect that the molecular structure of **1-O₂CPh** is similar to that of the derivatives of

Scheme 3. Syntheses of Cu(I) and Cu(II) Complexes



$[(\text{BPI})\text{CuX}]$ ($\text{X} = 2,6\text{-dimethoxybenzoate}$ and $3,4\text{-dimethoxybenzoate}$) (*vide infra*). To assign the oxidation state of the copper center, we performed X-band EPR measurement on **1-O₂CPh** in toluene at 25 K. The X-band EPR spectrum of **1-O₂CPh** revealed an axial pattern, consistent with a Cu(II) ($S = 1/2$) center.

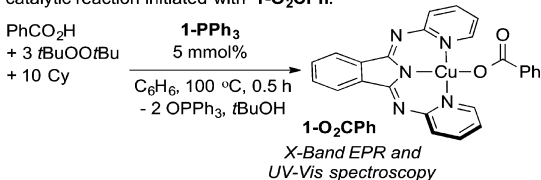
To isolate a discrete Cu(I) complex, $[(\text{PPh}_3)_2\text{Cu}(\text{OAc})]^{38}$ was allowed to react with NaBPI. The reaction in toluene at room temperature formed $[(\text{BPI})\text{Cu}(\text{PPh}_3)_2]$ (**1-PPh₃**) in 58% yield as an orange crystalline solid (Scheme 3). Compound **1-PPh₃** was characterized by multinuclear (^1H , ^{13}C , ^{31}P) NMR spectroscopy, FT-IR spectroscopy, and elemental analysis. With discrete Cu(I) and Cu(II) complexes in hand, we investigated the resting state of the catalyst.

The resting state of the copper species in the reaction between cyclohexane and benzoic acid catalyzed by **1-PPh₃** with *t*BuOO*t*Bu as oxidant was determined by UV-vis spectroscopy, X-band EPR spectroscopy, and independent synthesis of copper complexes.³⁰ A mixture of benzoic acid, cyclohexane, and *t*BuOO*t*Bu with 5 mol% **1-PPh₃** in benzene was allowed to react for 2 h at 100 °C. The UV-vis spectrum of this reaction mixture was identical to that of independently synthesized **1-O₂CPh** recorded in benzene.³⁰ Likewise, the X-band EPR spectrum of the reaction mixture collected at 25 K was identical to that of an authentic sample of **1-O₂CPh**.³⁰

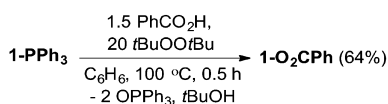
To assess the identity of this complex further, a stoichiometric reaction of **1-PPh₃** with benzoic acid (1.5 equiv) and *t*BuOO*t*Bu in the absence of cyclohexane was conducted at 100 °C for 0.5 h in benzene. This reaction afforded **1-O₂CPh** in 64% isolated yield (Scheme 4), as

Scheme 4. Determination of the Catalyst Resting State

A. Spectroscopic detection of the resting state of the catalytic reaction initiated with **1-O₂CPh**.



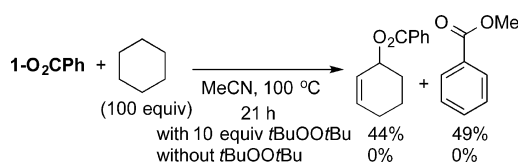
B. Independent generation of **1-O₂CPh** from **1-PPh₃**.



determined by FT-IR, X-band EPR spectroscopy, elemental analysis, and comparison of the material to **1-O₂CPh** synthesized independently from the salt metathesis reaction of **1-Cl** with NaO₂CPh. These data from the spectroscopic measurement of the copper species in the catalytic reactions and of the species formed independently from stoichiometric reactions strongly indicate that a copper(II)–benzoate complex is the resting state of the catalyst.

4. Elucidation of the Mechanism by Stoichiometric Reactions, Trapping Experiments, and Competition Experiments. To assess the role of **1-O₂CPh** in the catalytic reaction, we performed stoichiometric reactions of **1-O₂CPh** with the reaction components. The reaction of **1-O₂CPh** with cyclohexane was conducted in the presence of *t*BuOO*t*Bu at 100 °C for 21 h in acetonitrile (Scheme 5). The products consisted of cyclohex-2-en-1-yl benzoate (44%) and methyl benzoate (49%). These results are consistent with competitive

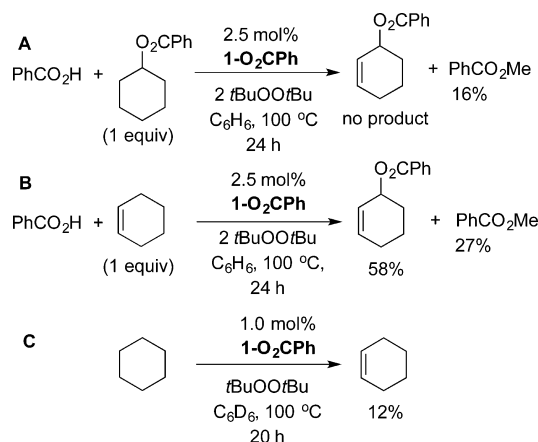
Scheme 5. Stoichiometric Reaction of **1-O₂CPh** with Cyclohexane with and without Peroxide



reactions of a cyclohexenyl radical and a methyl radical with **1-O₂CPh** to produce cyclohex-2-en-1-yl benzoate and methyl benzoate, respectively. The analogous reaction performed in the absence of *t*BuOO*t*Bu gave no product from reaction of the cyclohexane. These results show that the copper–benzoate does not react directly with the alkane. Instead, a species generated from copper and *t*BuOO*t*Bu reacts with the alkane.

To assess the sequence of bond-forming events in the catalytic ODC of cyclohexane, we conducted the reaction of cyclohexyl benzoate and cyclohexene (separately) (Scheme 6, A) with *t*BuOO*t*Bu and the copper catalyst. These two

Scheme 6. Experiments To Test the Sequence of C=C and C–O Bond Formation



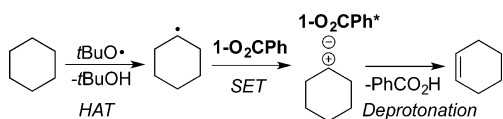
reactions reveal whether formation of the alkene occurs before or after formation of the C–O bond. The reaction of cyclohexyl benzoate, benzoic acid, and *t*BuOO*t*Bu with 2.5 mol% of **1-O₂CPh** at 100 °C for 24 h did not form cyclohex-2-en-1-yl benzoate. Instead, this reaction generated methyl benzoate (16%). The detection of methyl benzoate indicates that *tert*-butoxy radical was generated from the reaction of *t*BuOO*t*Bu with copper, but that this radical reacts more slowly with the cyclohexyl benzoate than it undergoes β -methyl scission to generate the methyl radical (which reacts with the copper–benzoate complex to form methyl benzoate).³¹

In contrast to the reaction of cyclohexyl benzoate, the reaction of cyclohexene with benzoic acid and *t*BuOO*t*Bu in the presence of 2.5 mol% **1-O₂CPh** generated the allylic ester. This reaction formed cyclohex-2-en-1-yl benzoate in 58% yield and methyl benzoate in 27% yield after 24 h at 100 °C (Scheme 6B). Moreover, the reaction of cyclohexane with *t*BuOO*t*Bu in the presence of 1 mol% of **1-O₂CPh** (based on *t*BuOO*t*Bu) in benzene-*d*₆ at 100 °C for 20 h (Scheme 6C) formed cyclohexene in 12% yield, with respect to cyclohexane, as determined by ^1H NMR spectroscopy. These results clearly indicate that ODC of cyclohexane to cyclohex-2-en-1-yl benzoate proceeds by initial conversion of the cycloalkane to

the cycloalkene, followed by oxidation of the cycloalkene to the final allylic ester product.

The mechanism for the initial conversion of cyclohexane to cyclohexene likely proceeds by abstraction of a hydrogen atom from cyclohexane by a *tert*-butoxy radical to generate a cyclohexyl radical, which undergoes oxidation to the alkene. The oxidation of alkyl radicals to olefins by copper–peroxide systems has been studied by Kochi^{32,39} and Walling.⁴⁰ Their studies imply that oxidation of the cyclohexyl radical formed in the current system likely generates cyclohexyl cation, which undergoes deprotonation to form the alkene. The deprotonation could occur by the anionic Cu(I) complex [(BPI)Cu(O₂CPh)][−] (**1-O₂CPh**[−]) (Scheme 7). The yield of allylic ester would then be a function of the relative rate of oxidation of the alkyl radical versus reaction of the alkyl radical with the copper carboxylate.

Scheme 7. Proposed Mechanism for the Conversion of Cyclohexane to Cyclohexene



After formation of cyclohexene, oxidation at the allylic position to form cyclohex-2-en-1-yl benzoate would occur through the mechanism of the Kharasch–Sosnovsky reaction.^{8,9,24,40–44} In this pathway, the allylic hydrogen is abstracted by a *tert*-butoxy radical, and the resulting allylic radical reacts with the copper carboxylate to form the allylic ester.

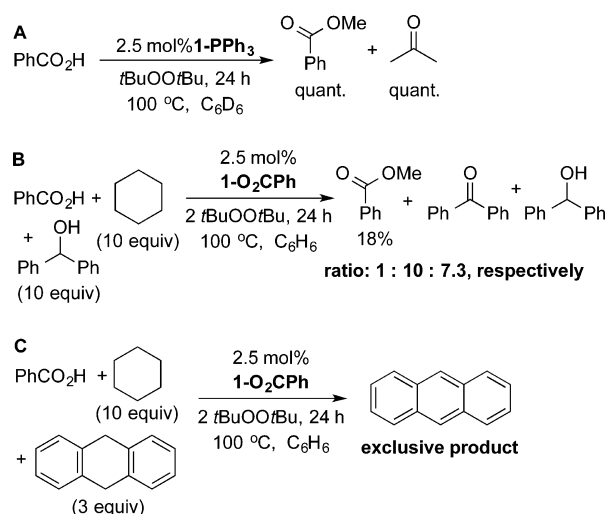
To detect for the possible formation of 1,3-cyclohexadiene or benzene from cyclohexene through a series of steps involving abstraction of the allylic hydrogen, oxidation of the allyl radical, and deprotonation of the allyl cation, the catalytic reaction of benzoic acid, cyclohexane, and *t*BuOO*t*Bu in the presence of **1-PPh₃** (2.5 mol%) in *d*₆-benzene (or *d*₃-MeCN) at 100 °C for 16 h was monitored by ¹H NMR spectroscopy. The result of the reaction revealed only cyclohex-2-en-1-yl benzoate and methyl benzoate as products in 40% and 14% yields, with respect to benzoic acid. Cyclohexadiene and benzene that could result from dehydrogenation of cyclohexene were not observed.

The stoichiometric and catalytic ODC of benzoic acid with cyclohexane forms methyl benzoate as the major side product. The observation of this product is consistent with the intermediacy of *tert*-butoxy radical. β -Methyl scission of a *tert*-butoxy radical is known to produce a methyl radical, and this radical would react with the resting-state **1-O₂CPh** to give methyl benzoate.

To evaluate the potential generation of *tert*-butoxy radical in the system, the standard catalytic reaction of benzoic acid in C₆D₆ was performed in the absence of cyclohexane (Scheme 8A). Without a source of an alkyl radical besides the one formed by β -methyl scission of [•]O*t*Bu, the reaction produced a quantitative yield of methyl benzoate and acetone (based on benzoic acid as limiting reagent). This high-yield formation of methyl benzoate from benzoic acid and *t*BuOO*t*Bu in the presence of **1-PPh₃** further supports the intermediacy of a transient *tert*-butoxy radical in the catalytic reaction.⁴⁵

As a final test of the potential intermediacy of *tert*-butoxy radical in the catalytic process, we conducted reactions in the presence of diphenylmethanol, a known trap for *tert*-butoxy

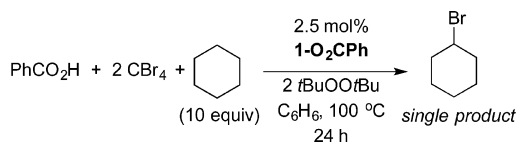
Scheme 8. Experiments To Probe the Intermediacy of *tert*-Butoxy Radical



radical,⁴⁶ and in the presence of 9,10-dihydroanthracene, which forms anthracene via hydrogen atom abstraction by alkoxy radicals. The catalytic reaction of cyclohexane, benzoic acid, and diphenylmethanol in the presence of **1-O₂CPh** produced methyl benzoate (18%), benzophenone, and diphenylmethanol in a ratio of 1:10:7.3 (Scheme 8B). The same reaction between cyclohexane and benzoic acid at 100 °C for 24 h in the presence of 9,10-dihydroanthracene produced anthracene as the exclusive product from the hydrocarbon reactants (Scheme 8C). The formation of benzophenone and anthracene is consistent with H-atom abstraction of the methine C–H bond of diphenylmethanol and a methylene C–H bond of dihydroanthracene by *tert*-butoxy radical to produce the organic products. The detection of methyl benzoate as an additional product, again, is consistent with β -methyl scission of a *tert*-butoxy radical under the catalytic conditions.

To assess the potential intermediacy of a cyclohexyl radical, the catalytic reaction of cyclohexane with benzoic acid was performed in the presence of CBr₄. This reaction exclusively formed bromocyclohexane (Scheme 9). The observation of

Scheme 9. Trapping of the Proposed Cyclohexyl Radical by CBr₄

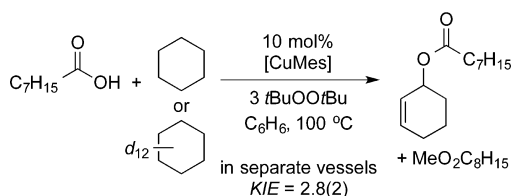


bromocyclohexane is further consistent with the formation of cyclohexyl radical by abstraction of a hydrogen atom from cyclohexane by a *tert*-butoxy radical in the catalytic reaction. In this case, the radical reacts with CBr₄ to form the alkyl bromide.^{47–49}

5. Kinetic Isotope Effect and Reactivity of the Alkyl Radical with Copper–Amidate and Copper–Benzoate. Parallel reactions were performed with cyclohexane and cyclohexane-*d*₁₂ to determine if cleavage of the C–H bond of the alkane is the turnover-limiting step of the copper-catalyzed ODC of cyclohexane. A comparison of the initial rates for catalytic ODC of octanoic acid with cyclohexane and cyclohexane-*d*₁₂ in separate vessels revealed a KIE value of

2.8 ± 0.2 (Scheme 10). This observed KIE value indicates that C–H bond cleavage is the turnover-limiting step.

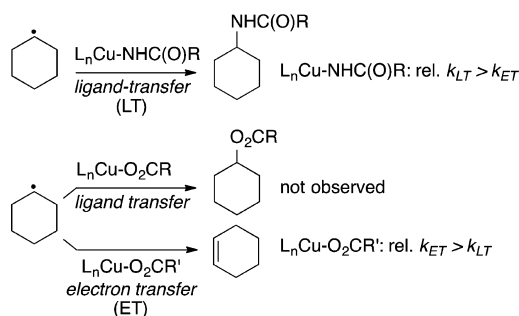
Scheme 10. Intermolecular ODC of Cyclohexane and Cyclohexene- d_{12}



In addition, a comparison of the rates of the catalytic reaction of octanoic acid with cyclohexane and cyclohexene revealed that the conversion of cyclohexene to cyclohex-2-en-1-yl octanoate is faster than the conversion of cyclohexane.³⁰ After 1 h, the reaction of octanoic acid and cyclohexene cleanly produced 40% of cyclohex-2-en-1-yl octanoate, whereas the reaction of octanoic acid with cyclohexane produced only 4% of cyclohex-2-en-1-yl octanoate and 2% of methyl octanoate. This result clearly indicates that abstraction of the C–H bond from cyclohexane, not from cyclohexene, is the turnover-limiting step in the catalytic ODC.

6. Effects of the Electronic Properties of Copper–Benzoate and Copper–Amidate Complexes on the Reaction of Alkyl Radicals. The roles of copper in the catalytic ODC of cyclohexane are closely related to those of copper in the catalytic amidation of cyclohexane we reported recently.²⁸ However, the two reactions form products containing different hydrocarbyl groups (alkyl vs allylic), and the difference between these groups likely stems from a difference in relative rates for reaction of the alkyl radical with the copper–benzoate and copper–amidate complexes. The alkyl radical can undergo electron transfer, or it can combine with a ligand at copper to form a product containing a new carbon–heteroatom bond (Scheme 11). Apparently, oxidation

Scheme 11. Ligand Transfer versus Electron Transfer of Alkyl Radicals in Copper–Amidate or Copper–Benzoate



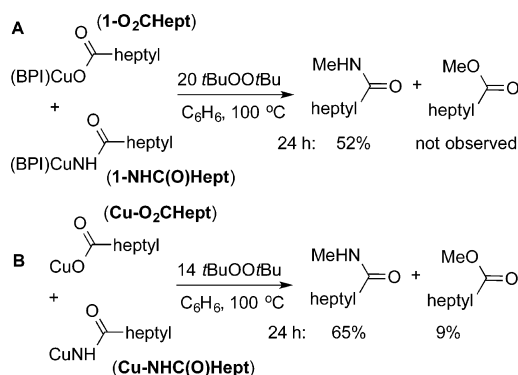
of the alkyl radical by the copper–benzoate is faster than reaction of the alkyl radical with the benzoate ligand, whereas oxidation of the alkyl radical by the copper–amidate is slower than reaction of the alkyl radical with the amidate ligand (Scheme 11).

This difference in relative rates could arise from a difference in redox potential of the benzoate and amidate complexes. A Cu(II)–benzoate complex, presumably, is less electron-rich than a Cu(II)–amidate complex. Therefore, the former complex could oxidize the alkyl radical to an alkyl cation faster

than the latter complex. Alternatively, the difference in relative rates could arise from differences in the rates of reaction of alkyl radicals with the Cu(II)–carboxylate and Cu(II)–amidate complexes.

To reveal the origin of the difference in formation of alkyl and allyl products with amide and carboxylic acid reagents we conducted a series of reactions in which a methyl radical is generated in the presence of a copper–carboxylate, amidate, or imidate complex. First, the reaction of a source of methyl radical ($t\text{BuOO}t\text{Bu}$) with a combination of [(BPI)Cu(NHC(O)[heptyl])] (**1-NHC(O)hept**) and [(BPI)Cu(O₂C[heptyl])] (**1-O₂Chept**) at 100 °C (Scheme 12A) was performed to assess

Scheme 12. Competition Reaction of Methyl Radical with Copper–Amidate and Copper–Carboxylate Complexes

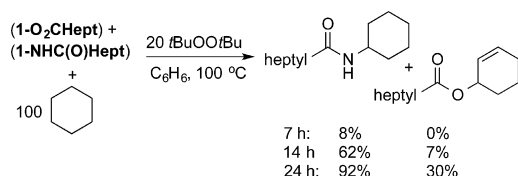


the ratio of products resulting from reactions of alkyl radicals with Cu(II)–amidate and Cu(II)–carboxylate complexes together. This reaction produced only MeNHC(O)[heptyl] (52% at 24 h); MeO₂C[heptyl] was not observed by GC. Thus, the rate of reaction of methyl radical with **1-NHC(O)hept** is faster than that with **1-O₂Chept**. Analogous reactions of methyl radical with a combination of **1-O₂CPh** and either [(BPI)Cu(NHC(O)Ph)] (**1-NHC(O)Ph**) or [(BPI)Cu(phth)] (**1-phth**) in the presence of $t\text{BuOO}t\text{Bu}$ (20 equiv) in benzene at 100 °C also showed that the reaction of methyl radical with **1-NHC(O)Ph** and **1-phth** is faster than that with **1-O₂CPh**.³⁰

Second, a competition reaction was performed between unligated [Cu(NHC(O)[heptyl])] and [Cu(O₂C[heptyl])] in the presence of $t\text{BuOO}t\text{Bu}$ at 100 °C in benzene (Scheme 12B) to probe the effect of the BPI ancillary ligand on the rate of reaction of the methyl radical with the Cu(II)–amidate and Cu(II)–carboxylate complexes. Like the reactions with the ligated copper complexes, the reaction of the unligated complexes with the source of Me• produced higher yields of MeNHC(O)[heptyl] than of MeO₂C[heptyl] throughout the reaction. The result of this experiment indicates that the rate of reaction of a methyl radical with a ligandless copper–amidate is faster than that with a ligandless copper–carboxylate.

Third, a competition reaction was performed with **1-O₂Chept** and **1-NHC(O)hept** in the presence of cyclohexane and $t\text{BuOO}t\text{Bu}$ at 100 °C in benzene (Scheme 13). Unlike a methyl radical, a cyclohexyl radical can form a carbon–heteroatom bond or convert to cyclohexene; carboxylation of the resulting alkene then forms an allylic ester. The reaction of the two copper complexes formed *N*-cyclohexyloctanamide in 92% yield and the allylic ester product cyclohex-2-en-1-yl benzoate in 30% yield. This result is consistent with faster reaction of an alkyl radical with a copper–amidate than with a copper–benzoate, but the origin of the absence of product

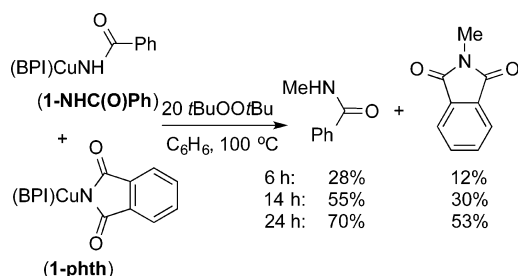
Scheme 13. Competitive Reaction of Cyclohexyl Radical with Copper–Amidate and Copper–Benzoate Complexes



from reaction of the allylic radical with the copper–amidate is unclear. We also observed the ODC of cyclohexane to cyclohex-2-en-1-yl benzoate only after an appreciable amount of 1-NHC(O)hept is consumed because 1-NHC(O)hept would react rapidly with the transient alkyl radical.

To investigate the effects of the nitrogen substituents on the reactions with alkyl radicals, we conducted the reaction of 1-NHC(O)Ph and 1-phth with *t*BuOO*t*Bu (20 equiv) in benzene at 100 °C for 24 h. This reaction formed higher yields of the MeNHC(O)Ph (70%) than of Me-phth (53%) (Scheme 14). The result of this competition experiment

Scheme 14. Reaction of Methyl Radical with Copper–Amidate and Copper–Imidate Complexes

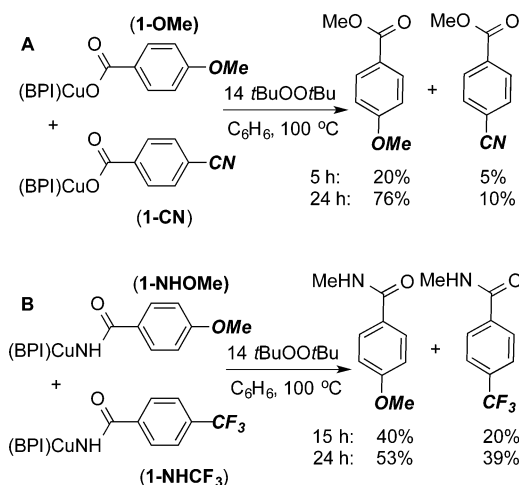


indicates that the reaction of the alkyl radical with 1-NHC(O)Ph is faster than that with 1-phth. This trend is consistent with faster reaction of an alkyl radical with the more electron-rich anionic ligand on copper.

To gain more systematic data concerning the electronic effects on the rates of reactions of alkyl radicals with the copper complexes, we studied reactions with a series of substituted benzoate complexes. Reactions of a methyl radical generated from *t*BuOO*t*Bu with a mixture of [(BPI)Cu(O₂C[C₆H₄-4-OMe])] (1-OMe) and [(BPI)Cu(O₂C[C₆H₄-4-CN])] (1-CN) were conducted at 100 °C in benzene (Scheme 15A). The result showed that methyl radical reacted faster with the electron-rich 1-OMe to produce the corresponding methyl 4-methoxybenzoate than with the more electron-poor 1-CN to produce methyl 4-cyanobenzoate. For example, at 24 h the reaction produced methyl 4-methoxybenzoate in 76% yield and methyl 4-cyanobenzoate in 10% yield.

To gain analogous information on the reaction of an alkyl radical with copper–amidates, the analogous experiment was conducted with [(BPI)Cu(NHC(O)[C₆H₄-4-OMe])] (1-NHOMe) and [(BPI)Cu(NHC(O)[C₆H₄-4-CF₃])] (1-NHCF₃). The reaction of *t*BuOO*t*Bu with these complexes at 100 °C in benzene (Scheme 15B) showed that the methyl radical reacts faster with the more electron-rich 1-NHOMe than with the more electron-poor 1-NHCF₃ to produce the corresponding product of *N*-methyl-4-methoxybenzamide (53%) at 24 h. The results of these competition reactions clearly demonstrate that alkyl radicals react faster with the more

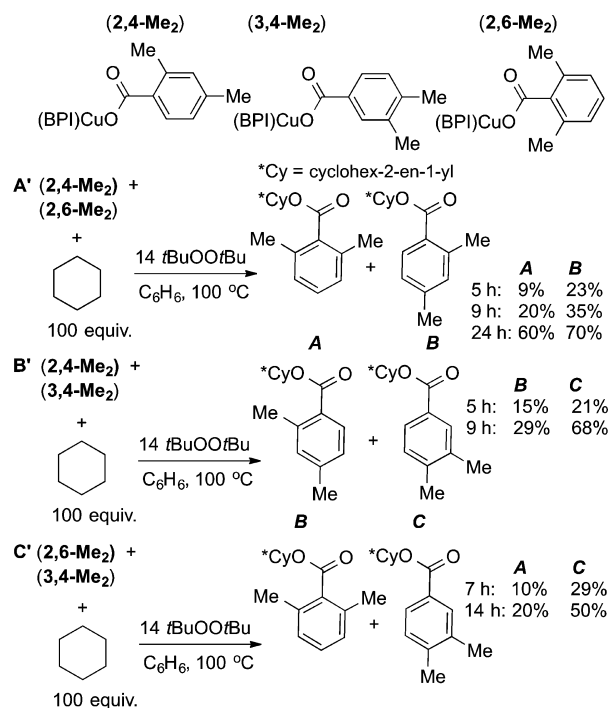
Scheme 15. Effect of Electronics on the Reactions of Methyl Radical with Copper–Benzoate and Copper–Amidate Complexes



electron-rich copper–benzoate and amidate complexes than with the more electron-deficient copper–benzoate and amidate complexes to form the corresponding *N*-alkyl and *O*-alkyl products, respectively.

7. Steric Effects on the Reaction of Alkyl Radicals with Copper–Benzoates. To elucidate the steric effect of aromatic ring of the carboxylate ligand in copper–benzoate complexes on the reactivity, we performed reactions of cyclohexane and *t*BuOO*t*Bu in the presence of a series of copper–benzoates containing methyl groups in the ortho, meta, and para positions: [(BPI)CuX], with X = 2,6-dimethylbenzoate (2,6-Me₂), 2,4-dimethylbenzoate (2,4-Me₂), and 3,4-dimethylbenzoate (3,4-Me₂). The results of these competition experiments are summarized in Scheme 16. The reaction with

Scheme 16. Effect of Aromatic Substituents on Copper–Benzoate Complexes on ODC of Cyclohexane



the combination of 2,4-Me₂ and 2,6-Me₂ formed a higher yield of cyclohex-2-en-1-yl 2,4-dimethylbenzoate than cyclohex-2-en-1-yl 2,6-dimethylbenzoate (Scheme 16A'). The reaction with a combination of 2,4-Me₂ and 3,4-Me₂ formed the corresponding cyclohex-2-en-1-yl 3,4-dimethylbenzoate in higher yields than it formed cyclohex-2-en-1-yl 2,4-dimethylbenzoate (Scheme 16B'). Lastly, the reaction with the combination of 3,4-Me₂ and 2,6-Me₂ produced higher yield of cyclohex-2-en-1-yl 3,4-dimethylbenzoate (40%) than of cyclohex-2-en-1-yl 2,6-dimethylbenzoate (20%) at 24 h (Scheme 16C'). Similar results were obtained from competition reactions between cyclohexane and *t*BuOO*t*Bu with a series of dimethoxybenzoate–Cu(II) complexes.³⁰

The difference in rates of reaction of the carboxylate complexes as a function of the steric properties could result from the effect on the conformation of these copper–benzoate complexes and overlap of the aryl π system with the carbonyl group. The molecular structures of 2,6-OMe₂ and 3,4-OMe₂ were determined by X-ray diffraction (Figure 1). The aryl ring

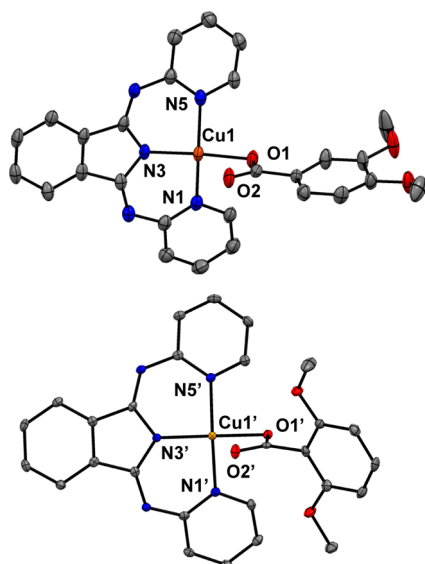
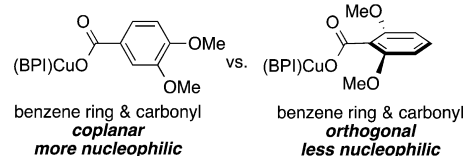


Figure 1. Molecular structures of [(BPI)Cu(3,4-OMe₂-C₆H₄)] (3,4-OMe₂) (top) and [(BPI)Cu(2,6-OMe₂-C₆H₄)] (2,6-OMe₂) (bottom) are shown with 50% thermal ellipsoid. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°) for 3,4-OMe₂: Cu1–N1 = 2.019(2); Cu1–N3 = 1.892(2); Cu1–O1 = 1.9443(18); N1–Cu1–N3 = 90.55(9); N3–Cu1–O1 = 168.23(9). Selected bond lengths (Å) and angles (°) for 2,6-OMe₂: Cu1'–N1' = 2.0074(17); Cu1'–N3' = 1.9017(17); Cu1'–O1' = 1.9721(14); N1'–Cu1'–N3' = 90.94(7); N3'–Cu1'–O1' = 167.63(7).

of the 2,6-dimethoxybenzoate is nearly orthogonal to the carbonyl group with a torsion angle of -76° , whereas the benzene ring of the 3,4-dimethoxybenzoate lies nearly in plane with the carbonyl group with a torsion angle of -163° . Thus, the aryl ring of 3,4-OMe₂ has more orbital overlap between the carbonyl and benzene π -systems than does that of the 2,6-disubstituted benzoate. This distortion from planarity of the 2,6-disubstituted benzoate makes it less nucleophilic (Scheme 17).⁵⁰ This reduced nucleophilicity is then responsible for the difference in the reactivity of copper–benzoate with the allylic radical to generate allylic benzoate products.

8. Observation of Oxidative Dehydrogenative Amination: Effect of Ligand and Nitrogen Source. The step that distinguishes the reactivity of copper-catalyzed ODC of

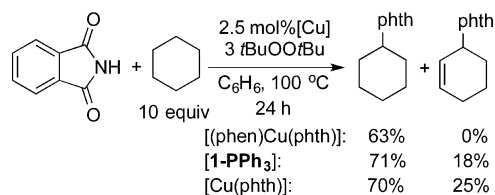
Scheme 17. Effect of Aromatic Substituents on the Conformation of Copper–Benzoate Complexes



cyclohexane and copper-catalyzed amidation of cyclohexane is the reaction of the transient cyclohexyl radical with a copper–benzoate versus a copper–amidate or copper–imide intermediate. Specifically, alkyl radicals react faster with copper–amidate and imide complexes than they do with copper–benzoates. Moreover, more electron-rich copper–amidate and benzoate complexes react faster with alkyl radicals than more electron-deficient copper–amidate and benzoate complexes. Lastly, the slower rate of reactions of alkyl radicals with copper–benzoate allows electron transfer to occur faster than ligand transfer, unless the alkyl radical is not able to form an alkene (i.e., a methyl radical). When the alkyl radical cannot form an alkene, ligand transfer occurs to form an O-alkyl product. Based on these hypotheses, we investigated copper-catalyzed oxidative dehydrogenative amination (ODA) of cyclohexane with electron-deficient amides. More electron-deficient copper–amidate and imide complexes would undergo slower reactions with an alkyl radical and faster electron transfer.

To this end, we conducted catalytic reactions of phthalimide and cyclohexane (10 equiv) in the presence of 2.5 mol% of [(phen)Cu(phth)], 1-PPh₃, and [Cu(phth)] (Scheme 18).⁵¹

Scheme 18. Formation of Alkyl and Allylic Imide from Cyclohexane

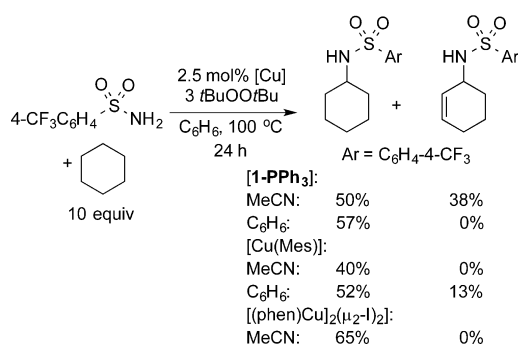


The reactions in the presence of 1-PPh₃ and [Cu(phth)] produced 18–25% of cyclohex-2-en-1-yl phthalimide and roughly 70% of *N*-cyclohexylphthalimide. The reactions conducted with 1-PPh₃ and [Cu(phth)] apparently occur by competitive ligand transfer and electron transfer to form a mixture of *N*-cyclohexylphthalimide and cyclohex-2-en-1-yl phthalimide, respectively. Conversely, the reaction catalyzed by [(phen)Cu(phth)] formed *N*-cyclohexylphthalimide (63%) and *N*-methylphthalimide (19%), and no cyclohex-2-en-1-yl phthalimide, as determined by gas chromatography, mass spectrometry, and ¹H NMR spectroscopy.

The catalytic reaction in the presence of [(phen)Cu(phth)] exclusively produced *N*-cyclohexylphthalimide and *N*-methylphthalimide, presumably from reaction of the methyl and cyclohexyl radicals with the resting-state species [(phen)Cu(phth)₂].²⁸ The preference of [(phen)Cu(phth)₂] to react with cyclohexyl radical by ligand-transfer is presumably because [(phen)Cu(phth)₂] is more electron-rich than the complexes 1-phth and [Cu(phth)₂]_n; thus, reaction of the alkyl radical with [(phen)Cu(phth)₂] occurs faster than electron transfer.

Previously, we reported the copper-catalyzed oxidative coupling of *p*-toluenesulfonamide with cyclohexane to generate the corresponding *N*-cyclohexyl-*p*-toluenesulfonamide.²⁸ To achieve ODA of cyclohexane, we reasoned that replacing *p*-toluenesulfonamide with the more electron-deficient 4-*CF*₃-benzenesulfonamide should decrease the rate of reaction of the alkyl radical with the ligand and increase the rate of oxidation of the alkyl radical. The reaction of 4-*CF*₃-benzenesulfonamide with cyclohexane and *t*BuOO*t*Bu in the presence of 2.5 mol% of **1-PPh**₃ in acetonitrile produced *N*-cyclohexyl-4-*CF*₃-benzenesulfonamide (50%) and *N*-(cyclohex-2-en-1-yl)-4-*CF*₃-benzenesulfonamide (38%) (Scheme 19). This result demonstrates that electron-deficient sulfonamides can form substantial amount of product from ODA of cyclohexane by the electron-transfer pathway.

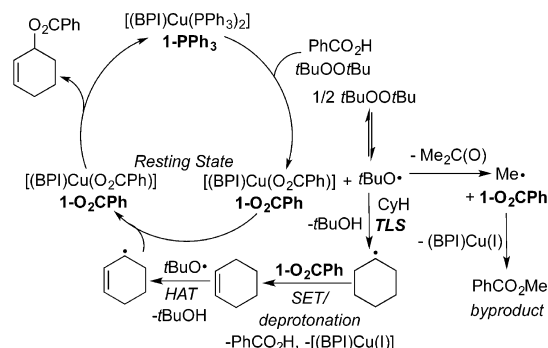
Scheme 19. Catalytic ODA of Cyclohexane with an Electron-Deficient Sulfonamide



The selectivity of the reaction of cyclohexane with *CF*₃-4-benzenesulfonamide in the presence of **1-PPh**₃ depended on solvent and supporting ligand (Scheme 19). The reaction in acetonitrile formed the mixture of alkyl and allylic amides just described, but the reaction in benzene generated exclusively cyclohexyl-4-*CF*₃-benzenesulfonamide (57%). The distribution of products from the reaction of *CF*₃-4-benzenesulfonamide and cyclohexane in the presence of “ligandless” copper generated from [Cu(Mes)] also depended on solvent, but with the opposite trend. The products of ODA were observed in benzene, but not in acetonitrile (Scheme 19). Like the reactions of phthalimide, the reactions of *CF*₃-4-benzenesulfonamide with cyclohexane in the presence of phen-ligated copper provided only the *N*-alkyl product (Scheme 19). This result again highlights the effect of the electronic properties of the supporting ligand on the relative rates to form *N*-alkyl and *N*-allyl products. This effect of ligand (i.e., BPI vs phen) on this selectivity reflects an opportunity to design ligands that favor ODA of unactivated alkanes.

9. Proposed Mechanism for ODC of Cyclohexane. A proposed mechanism for the catalytic ODC of cyclohexane to cyclohex-2-en-1-yl benzoate is presented in Scheme 20. In this pathway, catalysis is initiated by the decomposition of *t*BuOO*t*Bu by **1-PPh**₃ to produce a *tert*-butoxy radical and [(BPI)CuOtBu], which rapidly reacts with benzoic acid to form **1-O₂CPh** and *t*BuOH. The *tert*-butoxy radical can undergo reversible, secondary internal return to regenerate *t*BuOO*t*Bu or abstract a hydrogen atom from cyclohexane to generate a cyclohexyl radical. To form the unsaturated product, **1-O₂CPh** would oxidize the alkyl radical by one electron to form a carbocation, and the carbocation would undergo deprotonation by an anionic Cu(I) species [(BPI)Cu(O₂CPh)][−] to give

Scheme 20. Proposed Catalytic Cycle of Cu-Catalyzed ODC of Cyclohexane



cyclohexene and benzoic acid. The resulting cyclohexene would then undergo a second C–H abstraction by a *tert*-butoxy radical to give an allylic radical that reacts with **1-O₂CPh** to release the allylic ester product and regenerate a (BPI)Cu(I) species to complete the catalytic cycle. In a side reaction, the *tert*-butoxy radical would decompose to a methyl radical and acetone. The methyl radical would then combine with **1-O₂CPh** to produce methyl benzoate and a (BPI)Cu(I) species. The catalytic cycle for ODA of cyclohexane to form *N*-allyl products is presumably analogous to that of the catalytic ODC. This catalytic cycle would contain a copper–amidate resting state, based on mechanistic investigations of a related copper-catalyzed amidation of unactivated alkanes.²⁸

SUMMARY AND CONCLUSIONS

In summary, we have described a copper-catalyzed oxidative dehydrogenative carboxylation (ODC) of unactivated alkanes with a variety of benzoic acids to produce the corresponding allylic ester products. A measurement of kinetic isotope effects showed that the turnover-limiting step is C–H bond cleavage, and experiments to trap radical intermediates revealed that a transient *tert*-butoxy radical cleaves the C–H bond of the alkane to generate an alkyl radical. Reactions of alkyl radicals with a combination of Cu(II)–amidates and Cu(II)–benzoates revealed that the alkyl radical reacts faster with a Cu(II)–amidate than with a Cu(II)–benzoate to form *N*-alkyl products. Additional mechanistic investigations indicated that the electronic properties of the Cu(II)–X (X = amidate, benzoate) resting state contributes to the partitioning of the alkyl radical between ligand transfer to form the alkyl–heteroatom bond and electron transfer to oxidize the alkyl radical to an olefin, followed by oxidative carboxylation to produce an allylic ester. The reaction of the alkyl radical with a Cu(II)–amidate versus a Cu(II)–benzoate is the step that distinguishes copper-catalyzed amidation and copper-catalyzed ODC of the alkane.

This insight into the mechanism of ODC of cyclohexane led to preliminary observations of copper-catalyzed oxidative dehydrogenative amination of cyclohexane with electron-deficient nitrogen sources (i.e., phthalimide and an electron-deficient sulfonamide) to form *N*-allyl products. Current efforts are underway to discover reaction conditions to suppress ligand transfer and favor electron transfer to achieve high selectivity for a copper-catalyzed ODA of unactivated alkanes.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, characterization of compounds, and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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